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In the midst of the antimicrobial discovery conundrum: an overview

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Antimicrobials have been heralded as one of the most significant advances in modern medical history. Indeed, vaccination has led to the eradication of small pox, polio and the near elimination of measles in the U.S. [1,2]. Antibiotics are credited with saving the lives of critically ill patients suffering from otherwise-lethal bacterial infections as well as enabling surgical intervention and survival of immunocompromised patient populations [3–5]. Despite these successes, neither vaccine nor antibiotic development has kept pace with the emergence of new bacterial pathogens or antibiotic resistance, creating a healthcare crisis that is well recognized by healthcare personnel but only beginning to be appreciated by lawmakers and the public.

Ironically, one could argue that the effectiveness of early vaccines and antibiotics are, themselves, at the heart of today's antimicrobial pipeline void. After all, their short-course dosing, impressive efficacy, limited side effects, and low-cost set the bar for which future antibacterials are measured; a profile that is unsustainable from both a practical and economic stand point, as evidenced by the current situation. It is intriguing to consider what the requisites for approval of a new antibacterial agent would look like today if penicillin demonstrated 40% efficacy or how lucrative the industry would be if it was priced at $25 in the 1940s.

But that is not the case, rather, in the face of well-documented enormous clinical trial costs and low return on investment most of large-pharma has severely reduced or out-right eliminated infectious disease research and development in lieu of pursuing more lucrative therapeutics and who could blame them? While, as discussed below, agencies have provided incentives for large pharma reinvestment in the antimicrobial space, the damage has already been done in terms of both the immediate collapse in the antibacterial pipeline but also with respect to the long-term consequences associated with the loss of an entire generation of antimicrobial researchers. With regard to the latter it is very telling that the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), which has served as the world's premiere meeting on antimicrobial research for the past 54 years, has gone from a record high attendance of 16,216 participants in 1999 [6] to extinction as a stand-alone meeting (Co-locating with the American Society for Microbiology General meeting in 2016). Not only are we facing an anemic antimicrobial portfolio, we are hemorrhaging the very expertise needed to improve the situation.

The current situation is by no means purely a function of profit-driven industrial neglect. Rather, it is also a consequence of years of difficult regulatory hurdles combined with limited public research dollars. As noted above, the efficacy of past generations of antibiotics has justifiably 'conditioned' regulatory agencies to expect the same, or better, from new antimicrobials. But the lack of effective vaccines and antibiotics to combat multi-drug resistant bacteria and emerging pathogens make it painfully clear that the current system is broken and changes are urgently needed. As discussed below, recent activities both in the public and private sectors allow one to be cautiously optimistic that such changes are beginning to take place, but also indicate that the conventional antimicrobial discovery and development paradigm is undergoing a radical transformation.

Priming the pump

Historically, basic academic research has fueled therapeutic target ideas for biotech-associated discovery and early proof-of-concept studies. These results are then fed to pharmaceutical companies with the resources to refine/optimize a given agent, perform clinical trials, and ultimately market those products for clinical use. In the antimicrobial space, this model is broken at nearly every level.

The U.S. healthcare system is currently being ravaged by the ESKAPE bacterial pathogens [7], yet research dollars

dedicated to study and, consequently, provide a healthy conduit for innovative strategies for the therapeutic intervention of those organism's is dwarfed by research dollars directed toward studies of HIV, alcoholism, etc. Indeed, in their survey of NIAID funding dollars Kwon *et al*., gravely pointed out that '*from a mortality stand point, even though in the United States MRSA and HIV may be on par with each other, the research dollars invested shows a stark difference* [$1,565 vs. $72,000 per death, respectively]' [8]. Similarly, a review of the U.S. Department of Health and Human Services Research Portfolio Online Reporting Tools (NIH RePORT) indicates that the number of antibacterial development research awards languish 3.7 (±0.46) to 1 behind that of antiviral development projects, despite initiatives by the Infectious Diseases Society of America [9], and others, to reinvest in new antibacterial research and development (Figure 1). The good news is that the number of NIH awards dedicated to antibacterial development research has increased 3.3-fold from 1997 to 2014, which has marginally outpaced increases in both the number of antiviral development awards (2.7-fold increase) and the NIH budget (2.4-fold increase) during this same time span. But, ultimately, these awards must be translated to projects that can be directly or indirectly (via biotech) advanced to clinical trials to see the light of day.

The cost of doing business

At issue, very few large pharmaceutical companies can, or want to, engage in early research and discovery or even move a promising early-stage antibacterial agent forward. The reasons for this, as mentioned above, have been mostly governed by a low return on investment for antibiotics in comparison to blockbuster drugs such as Lipitor, Humira, and Sovaldi. Yet a survey of the earning properties of several representative antibiotics that have recently cycled through their patent life make it clear that antibiotics are capable of generating earnings of >$1B annually, despite competition, suggesting that the market is far from saturated (Figure 2). However, two issues have severely crippled their full earning potential. First, public health rightfully mandates good stewardship practices, which by their very nature limits antibiotic consumption as a means to preserve their efficacy. Second, like all therapeutics, earnings are also severely impacted by patent expiration, as evidenced by Zosyn annual sales prior to (>$1B annually) — and following ($400M annually) — the launch of generics by Hospira, Novartis, Aurobindo, and Istitutio.

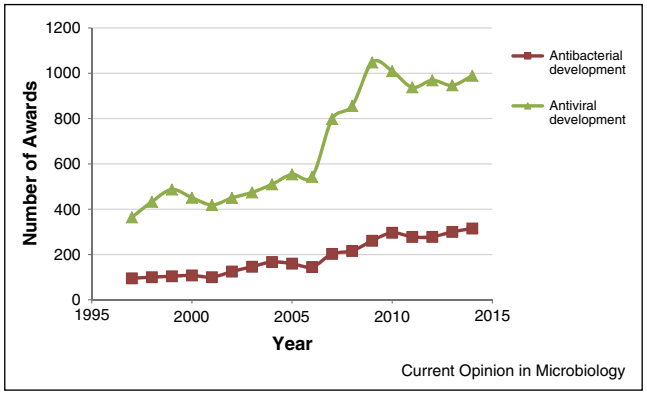
In that regard, it is worthwhile noting that The Patent Act of 1790 provided patent exclusivity for 14 years from the date of *issuance* [10]. Today, 225 years later, patent exclusivity is provided for 20 years from the date of *filing*, which when considering the amount of time to issuance essentially equals 17.6 years of protection; the 2013 U.S. Patent and Trademarks Performance & Accountability Report indicates that it takes an average of 29.1 months for a patent to issue [11]. By comparison the Sonny Bono Copyright Term Extension Act of 1998 extended copyright terms for articles in the U.S. to the life of the author plus 70 years [12]. It is difficult to reconcile how the document you are currently reading, a poem, or song lyrics should be deemed more important than a therapeutic agent in terms of protective exclusivity. As described below, the Food and Drug Administration (FDA) has begun taking steps to address this disconnect.

Bridging the gap

So how can antimicrobials become a more attractive investment? Simple economics teaches that maximal product profitability is achieved by minimizing production costs and maximizing revenue. A comparison of the risk-adjusted net present value (rNPV) of therapeutics, which essentially measures the overall incentive for pursuing a project based on cost associated with delivering an agent to market in conjunction with the agent's revenue, indicates that antibiotics and bacterial vaccines rank very low in comparison to other therapeutic areas [13]. Two obvious approaches to improve the rNPV of antimicrobials are to reduce cost of production and/or improve revenue.

Clinical trials represent the most expensive component of getting an agent to market; estimates indicate that they account for ≥90% of a drug's development costs with a price tag of approximately $1.3–$5.8 billion [14]. Reducing antimicrobial clinical trial costs would essentially reduce production cost and improve their rNPV. In that regard, recent initiatives championed by Rex, Eisenstein and colleagues propose to implement a 4-tier clinical trial system that for practical purposes is certainly needed, particularly for multidrug resistant bacterial pathogens

Figure 1



Plotted are the numbers of active research awards (*Y*-axis) identified per year (*X*-axis) within NIH Research Portfolio Online Reporting Tools database (NIH RePORT; http://report.nih.gov/index.aspx) using the search terms 'antibacterial development' or 'antiviral development'.